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Titanium(IV) Isopropoxide Mediated Synthesis of Pyrimidin-4-ones

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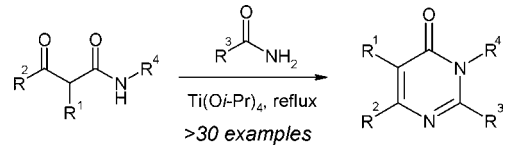
ABSTRACT



A novel, one-step method for the synthesis of tri- and tetrasubstituted pyrimidin-4-ones is reported. This method involves a titanium(IV)-mediated cyclization involving two sequential condensations of primary and β-ketoamides. The reaction is operationally facile, readily scalable, and offers rapid entry into differentially substituted pyrimidin-4-one scaffolds. The high functional group compatibility allows for substantial diversification in the products generated from this transformation.

The pyrimidin-4-one scaffold is well represented in natural and pharmaceutically relevant chemical matter. Physiochemically, this moiety represents an excellent drug-like template with which structurally diverse analogues can be generated and assessed. As such, this scaffold has shown immense value in the context of drug discovery, manifested through its presence in marketed drugs and clinical candidates (Figure 1). For instance, Isentress (**3**) and Risperidone (**4**) are marketed for the treatment of Schizophrenia and HIV, respectively.[1] The additional examples depicted span a variety of clinical indications and therapeutic targets.[2−7] Additional synthetic procedures to access these structures could allow for even greater exploitation of this chemical template.

While a variety of methods have been developed for the synthesis of bicyclic quinazolinones and tetrahydroquinazolinones, the known methods to prepare analogous differentially and/or tetrasubstituted pyrimidin-4-ones are limited. The most

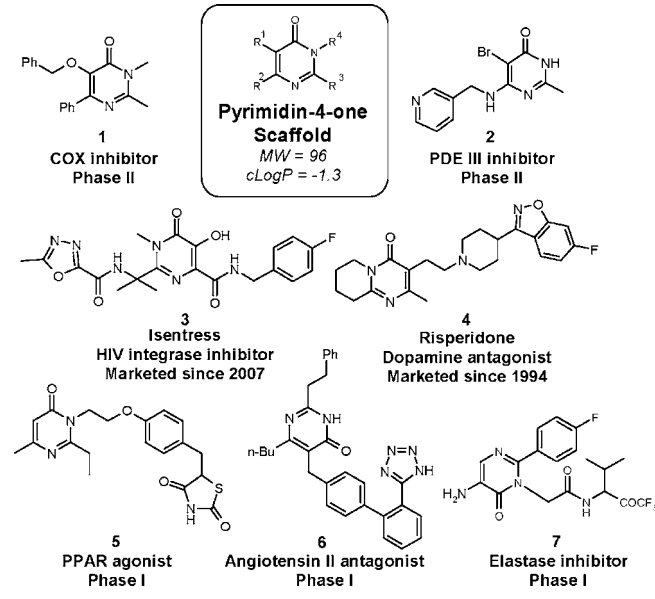


Figure 1. Pharmaceutically active pyrimidin-4-ones.

(1) Madaan, V. *Drugs Today* **2009**, *45* (1), 55–62.
(2) Nugent, R. A.; Schlachter, S. T. *PCT Int. Appl.* 1995, WO9511235A1.
(3) Bagli, J.; Bogri, T.; Palameta, B.; Rakhit, S.; Peseckis, S.; McQuillan, J.; Lee, D. K. H. *J. Med. Chem.* **1988**, *31*, 814.
(4) Belyk, K. M.; Morrison, H. G.; Jones, P.; Summa, V. *PCT Int. Appl.* 2006, WO2006060712A2.
(5) Madhavan, G. R.; Chakrabarti, R.; Vikramadithyan, R. K.; Mamidi, R. N. V. S.; Balaraju, V.; Rajesh, B. M.; Misra, P.; Kumar, S. K. B.; Lohray, B. B.; Lohray, V. B.; Rajagopalan, R. *Bioorg. Med. Chem.* **2002**, 2671.
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commonly employed routes are depicted in Figure 2. Route A involves the condensation of a Pinner-derived amidine with a β-ketoester to generate the pyrimidin-4-one scaffold but generally suffers from low yields and often poor "*O*" vs "*N*" selectivity in the subsequent alkylation step.[8,9] While Route B avoids this difficult alkylation, it is not without problems including low yields, scope limitation (restricted to malonyl dichlorides, R2 = H), and long reaction times.[10] Routes C−E share the underlying difficulty of enamine preparation which, in turn, is used to generate linear precursors such as an enamide ester (Route D) or an enediamide (Route E) prior to ring formation. Although many methods have been published for these transformations, they are generally low yielding and highly substrate dependent.[11,12] During the course of this work, these routes were evaluated to assess feasibility for rapid analogue generation and were found to be inadequate in some or all of the following aspects: functional group compatibility, incorporation of structural diversity, scalability, number of steps, and yields. In this paper, a highly efficient method for the preparation of differentially and tetrasubstituted pyrimidin-4-ones from β-ketoamide and primary amides mediated by titanium(IV) isopropoxide is disclosed.

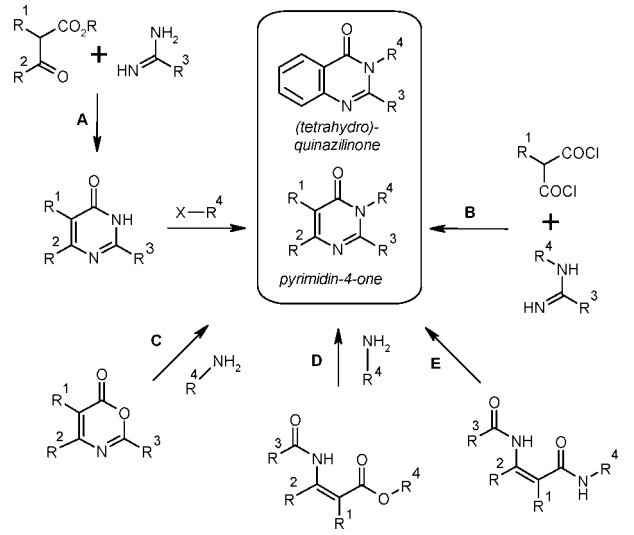
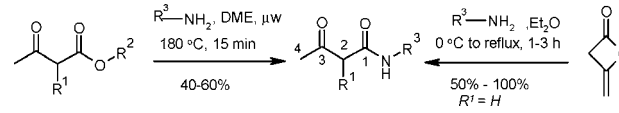


Figure 2. Common pyrimidin-4-one synthetic methods.

Access to a diverse collection of starting materials is critical to render any method as practical. While many primary amides are commercially available, the same cannot be said for β-ketoamides. As such, β-ketoamides were initially prepared using a two-step process coupling amines with β-ketoacids (not pictured), but this tactic resulted in low yields.[13] A more concise approach was then exploited: microwave irradiation of β-ketoesters with amines provided β-ketoamides directly in reasonable yields (Scheme 1).[14] This method is compatible with a variety of functionalities and allows for rapid access to the required β-ketoamides.[15] Alternatively, preparation of β-ketoamides devoid of C-2 substitution was achieved in high yields upon treatment of diketene with various amines.[15]

Scheme 1. Preparation of β-Ketoamides



Pyrimidin-4-one formation was realized through the titanium(IV) isopropoxide mediated union and cyclization of β-ketoamides and primary amides. A variety of alternate Lewis acids were screened to identify a suitable activator for this transformation, although none facilitated pyrimidin-4-one formation.[16] Ti(O*i*-Pr)$_4$ is a versatile reagent uniquely suited for this one-pot transformation, acting as both a Lewis acid, which activates otherwise poorly nucleophilic amides, and a mild dehydrating reagent. The relatively mild nature of this reagent suggested a high degree of functional group tolerance could be achieved. As this trait is paramount for any methodology to be employed in a pharmaceutical setting, an initial screening was conducted to assesses functional group tolerance (Figure 3). Unoptimized conditions (including use of a large excess of Ti(O*i*-Pr)$_4$, 15 equiv, and primary amide, 4 equiv) were used to clearly demonstrate this tolerability as unprotected N−H heterocycles (**10a**−**c**), phenols (**10g**),[17] and basic moieties (**10c, 10d**, **10f**) did not hinder the reaction. Even extremely electron-rich aromatic amides such as thiophene and oxazole proceeded smoothly (**10e** and **10f**). Importantly, the crystallinity of thiophene **10e** allowed for structural verification by X-ray crystallography and, thus, unambiguous regiochemical confirmation (Figure 4). Confident that the method would tolerate structural diversity, focus then shifted to optimization.

Initial attempts were made to reduce the requisite stoichiometry of Ti(O*i*-Pr)$_4$ by partially replacing with high boiling solvents such as 1,2-dichloroethane, toluene, and xylenes; however, no obvious advantage was observed for

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(9) Salimbeni, A.; Canevotti, R.; Paleari, F.; Poma, D.; Caliari, S.; Fici, F.; Cirillo, R.; Renzetti, A.; Subissi, A.; Belvisi, L.; Bravi, G.; Scolastico, C.; Giachetti, A. *J. Med. Chem.* **1995**, *38*, 4806.
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(12) Takahashi, T.; Hirokami, S.; Nagata, M. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2653.
(13) Grayson, D. H.; Tuite, M. R. *J. Chem. Soc., Perkin Trans. 1* **1986**, 2137.
(14) Addition of ethanol aids in absorption of microwave irradiation.
(15) See Supporting Information for general procedure.
(16) (a) Other Lewis acids tried [H^+, Sc(Tf)$_3$, $ZnCl_2$, Zn(Tf)$_2$, $MgSO_4$, Al(O*i*-Pr)$_3$, Zr(OEt)$_4$] generated no detectable/trace amounts of product by LCMS analysis. (b) Han, C.; Lee, J. P.; Lobkovsky, E.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2005**, *127*, 10039.
(17) It is known that the transesterification of titanium(IV) isopropoxide is known to be kinetically slow: Paquette, L. *Handbook of reagents for organic synthesis - Activating agents and protecting groups*; John Wiley & Sons: New York, 1999; pp 389−394.

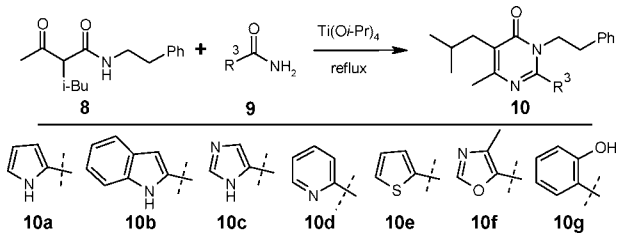


Figure 3. Synthesis of heterocycle-containing pyrimidin-4-ones. All products isolated and characterized; yields not determined

inclusion of such solvents. Importantly, the observation that the starting materials were readily dissolved in Ti(O*i*-Pr)$_4$ alone at elevated temperatures led to the minimization of the stiochiometry to just 4 equiv. The amount of primary amide was also lowered (1.2 equiv) without diminishing yields, and the reaction time was reduced to 24 h. Because the unoptimized conditions also included a workup procedure that stifled crude isolation and purification (distillation followed by messy aqueous workup and chromatography), rigorous optimization was required. Release of the organic material from the resultant titanium salts seemed to be a likely cause of the isolation difficulties. It was discovered that an acidic aqueous quench (2 N HCl) of the reaction followed by addition of toluene (with prolonged phase separation) ameliorated this problem. Further aqueous extraction with dichloromethane was required to complete the mass balance recovery. This two-step process allowed for facile chromatographic purification of the product pyrimidin-4-ones. These modifications resulted in an operationally facile and robust experimental procedure affording high isolated yields.[15]

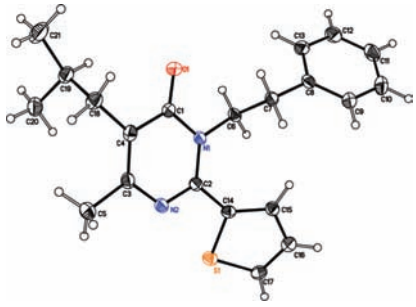
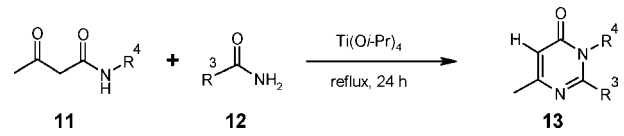


Figure 4. ORTEP representation for compound **10e**.

Initial scope exploration focused on unsubstituted β-ketoamides while varying the R4 group. Table 1 details the exemplars of β-ketoamides with differing substitution at the amide nitrogen (entries 1−4). Application of the optimized reaction conditions led to isolation of the desired pyrimidin-4-ones in reasonable yields. Condensation with benzamide (entry 4) demonstrates that this method tolerates inherently poor nucleophiles such as aryl amides. However, sterically bulky groups such as *i*-propyl (entry 2) and *c*-propyl (entry 3) are detrimental to the reaction resulting in lower yields.

The scope of the primary amide was also investigated with a wide variety of aliphatic and aromatic substituents (R3). Generally, the yields are moderate to high irrespective of the steric and electronic nature of the substituent (entries 5−14). An exception was observed with pivalamide (entry 9) where the bulky *tert*-butyl group exceeds the upper limit of steric tolerance for this transformation. Notably, the presence of heterocycles did not diminish the yields in spite of their potential to chelate with the Ti center (entries 11−14).

Table 1. Scope Exploration: Variation of R^3 and R^4



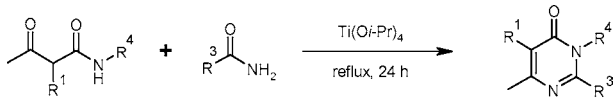
entry	R^4	R^3	**13** (yield %)
1	$(CH_2)_2Ph$	Ph	**13a** (64)
2	*i*-Pr	Ph	**13b** (7)
3	Cy	Ph	**13c** (42)
4	Ph	Ph	**13d** (38)[a]
5	$(CH_2)_2Ph$	Me	**13e** (22)
6	$(CH_2)_2Ph$	Et	**13f** (41)
7	$(CH_2)_2Ph$	*i*-Pr	**13g** (63)
8	$(CH_2)_2Ph$	Cy	**13h** (55)
9	$(CH_2)_2Ph$	*t*-Bu	**13i** (trace)[b]
10	$(CH_2)_2Ph$	Bn	**13j** (63)
11	$(CH_2)_2Ph$	4-pyridyl	**13k** (60)
12	$(CH_2)_2Ph$	2-pyrizyl	**13l** (54)
13	$(CH_2)_2Ph$	2-furyl	**13m** (74)
14	$(CH_2)_2Ph$	2-thienyl	**13n** (72)

[a] Reaction conversion was higher; purification problematic. [b] Product not isolated; trace product seen in LCMS.

The scope of the methodology was further expanded through the synthesis of tetrasubstituted pyrimidin-4-ones with R1 substitution arising from the β-ketoamide (Table 2). Yields did not suffer as a result of this functionalization; in fact, substitution at this position generally led to a considerable increase in isolated yield (compare Table 1, entry 1, and Table 2, entry 1), the rationale for which is discussed below. Interestingly, aliphatic and aromatic primary amides performed similarly (entries 1 and 2 vs 4 and 5), as the electronic nature of the benzamides had little bearing on the reaction outcome (entries 6−8).

Finally, the scalability of this methodology was demonstrated with the synthesis of highly functionalized pyrimidinone **17** (Scheme 2). The synthesis commenced with commercially available diketene, which, upon treatment with phenethylamine, produced β-ketoamide **11a** in quantitative yield. **11a** (127 g) was condensed with 3-fluoro-2-hydroxybenzamide[18] using 15 equiv of titanium tetraisopropoxide (unoptimized conditions) generating the pyrimidin-4-one product. The phenol was directly benzylated to produce **16**

Table 2. Preparation of Tetrasubstituted Pyrimidin-4-ones

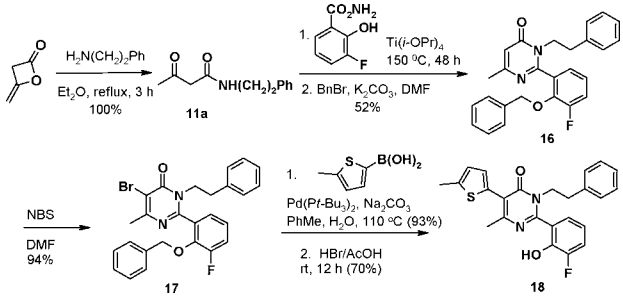


14 12 15

entry	R^1	R^4	R^3	**15** (yield %)
1	Me	$(CH_2)_2Ph$	Ph	**15a** (79)
2	Et	$(CH_2)_2Ph$(*o*-F)	Ph	**15b** (66)
3	Ph	$(CH_2)_2Ph$	Ph	**15c** (42)
4	Me	$(CH_2)_2Ph$	Et	**15d** (79)
5	Et	$(CH_2)_2Ph$(*o*-F)	Et	**15e** (61)
6	Me	$(CH_2)_2Ph$	4-OMe-Ph	**15f** (65)
7	Me	$(CH_2)_2Ph$	4-F-Ph	**15g** (84)
8	Me	$(CH_2)_2Ph$	2-furyl	**15h** (74)

(133 g) in 52% for two steps. Bromination of pyrimidin-4-one **16** offered a handle to introduce a fourth substituent at an alternate stage in the synthesis. Suzuki coupling with 5-methylthiophene boronic acid yielded **17**, and subsequent acidic debenzylation completed the synthesis of **18** (40 g) in six steps and 32% overall.

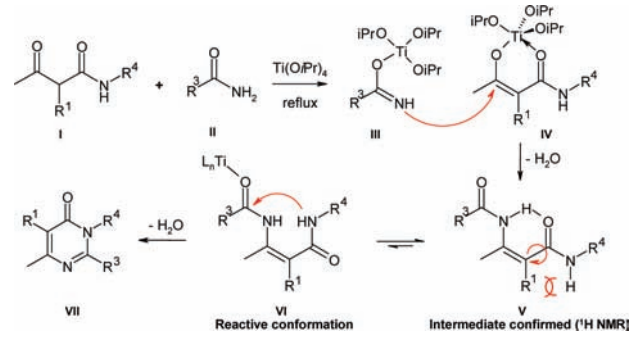
Scheme 2. Scalability of Pyrimidin-4-one: Scale-up of **18**



A proposed reaction mechanism is detailed below (Scheme 3). Titanium tetraisopropoxide is likely to chelate the primary amide **II** generating **III**, thus increasing its nucleophilicity. β-Ketoamide **I** could form a bidentate chelated intermediate **IV** augmenting its electrophilicity. The resultant enamine **III** then condenses with the chelated β-ketoamide **IV**, with subsequent dehydration (facilitated by the metal), generating the enediamide **V**. The formation of intermediate **V** has been confirmed by isolation and confirmation with LCMS and 1D/2D NMR experiments. The presence of excess titanium allows for another chelation event with enediamide **V**/**VI** and sets the stage for a second, intramolecular, condensation. The nucleophilic amide nitrogen attacks the pendant carbonyl, and subsequent dehydration generates the product pyrimidin-4-one, **VII**.

(18) For synthesis of 3-fluoro-2-hydroxy benzamide, see: patent WO2007062370A2.

Scheme 3. Proposed Reaction Mechanism



While no rigorous studies were undertaken explicitly to elucidate the underlying mechanism of this transformation, the proposed reaction mechanism above is based on the literature, substrate trends, and observed intermediates. For example, the negligible conversion with pivalamide (Table 1, entry 9) demonstrates that the initial bimolecular condensation is impeded by the sterics and suggests that this is the rate-determining step, a notion also supported by the lack of build-up of **V** during the reaction. Moreover, yields trend higher for *substituted* β-ketoamides (R1 $\neq$ H). This would indicate intermediate **V**, stabilized by an intramolecular hydrogen bond, would require a 180° bond rotation to populate the reactive conformation in which the reacting atoms are in close proximity. This rotation would be more energetically favored upon the introduction of R1 substitution due to 1,3-allylic strain. Although not conclusively proven, these data are supportive of the proposed mechanism above.

In conclusion, we have developed a novel preparation of pyrimidin-4-ones. This method utilizes a double condensation of two distinct amides facilitated by titanium tetraisopropoxide. The pyrimidin-4-one formation is accomplished through the ability of Ti(O*i*-Pr)$_4$ to function dually as a Lewis acid and dehydrating agent in the same transfomation. The relatively mild nature of the method tolerates a wide array of functionality and allows for rapid and efficient entry into tri- and tetrasubsituted pyrimidin-4-ones in a single step from simple reagents. The procedure was also demonstrated to be amenable for multigram synthesis. The pharmaceutical relevance of the pyrimidin-4-one scaffold coupled with the structural diversity that is accessible via this method will allow for widespread application of this technology.

Acknowledgment. We thank Robert Trout, Arun Kaura, Art Shu, and Thomas Ku for their assistance.

Supporting Information Available: Experimental procedures and characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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